MOLECULAR LIBRARIES SCREENING CENTERS NETWORK (MLSCN)

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THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS RFA

The Institutes and Centers (ICs) of the NIH invite applications from investigators interested in participating in an NIH Roadmap pilot program to establish the Molecular Libraries Screening Centers Network (MLSCN). The MLSCN will be a national resource capable of providing innovative high throughput molecular screening (HTS) approaches for the identification of small organic molecules (compounds) that are active in biological assays, and synthetic chemistry to improve the utility of these molecules as bioactive probes for in vitro, and potentially in vivo, studies of normal and abnormal physiology of cells, organs, model systems, and/or organisms.

The over-arching goal of the MLSCN is to screen large numbers of compounds to identify and subsequently optimize small molecules that selectively interact with specific biological targets so

that they may be used as probes to understand the function of newly characterized proteins, and to analyze physiological processes, cellular phenomena, and disease mechanisms. NIH's primary objective for this new public sector screening effort is to identify compounds that will constitute a new set of research tools for use by scientists in both the public and private sector. In addition, it is anticipated that some of these compounds will be used by both public and private sector scientists as chemical platforms that may lead to new therapeutics. Accordingly, NIH intends that all of the data and information generated by the MLSCN will be made publicly available in a new database to be known as PubChem. In this regard, NIH recognizes that there are significant issues concerning intellectual property rights with respect to patentable inventions developed during the MLSCN program. This subject is discussed more fully below. Within this context however, it is NIH's hope that inventors will exercise any intellectual property rights retained on inventions developed as part of the MLSCN program in a way that will promote wide accessibility to and further development of the resources that are generated.

Applications are invited from groups that have the interest and capabilities to develop and/or expand their assay development/optimization, screening, and synthetic chemistry operations as well as groups with established capabilities in these domains.

BACKGROUND

The NIH Roadmap is a series of new initiatives designed to pursue major opportunities and gaps in biomedical research that no single NIH institute could tackle alone but which the agency as a whole can address to make the biggest impact possible on the progress of medical research and to catalyze changes that will serve to transform new scientific knowledge into tangible benefits for public health (http://nihroadmap.nih.gov/). The Molecular Libraries and Imaging Initiative is one of the components comprising the Roadmap theme of 'New Pathways to Discovery', the goal of which is to build a better "toolbox" to use in understanding the many interconnected networks of molecules that comprise cells and tissues, their interactions, regulation, and the combination of molecular events that lead to disease. This Initiative will offer a publicly available database of biological information on small organic molecules, and public access to these molecules by the scientific community, to promote their use as chemical probes to study cellular pathways in greater depth and to provide new ways to explore the functions of major components of the cell in health and disease. It is anticipated that the Molecular Libraries and Imaging Initiative will: 1) produce research tools (molecular probes and novel assays) to facilitate studies of biology and pathophysiology, and that these tools will enable and catalyze the identification of novel targets for therapeutic intervention; and 2) accelerate the discovery of biomarkers to monitor disease progression and predict treatment response (http://nihroadmap.nih.gov/molecularlibraries/index.asp).

The MLSCN is a major component of the Molecular Libraries Initiative. Other components include: 1) the NIH Small Molecule Repository, a publicly available repository of 100,000-500,000 chemically diverse small organic molecules of both known and unknown activities (see http://grants.nih.gov/grants/guide/notice-files/NOT-RM-04-003.html); 2) PubChem, a public sector database that will archive the chemical structures and biological data generated by the MLSCN; and 3) the development of related technologies. The technology development initiatives will: (a) enhance the chemical diversity of small molecules; (b) facilitate the development and adaptation of innovative target- and phenotype-based assays that can be automated and considered for screening at the MLSCN; (c) develop new robotics and instrumentation for screening; and (d) stimulate the development of predictive ADME/toxicology (absorption, distribution, metabolism, and excretion/toxicology) assays and algorithms. The MLSCN also interacts with the Molecular Imaging Initiative (http://nihroadmap.nih.gov/molecularlibraries/index.asp).

An overview of how the MLSCN interacts with the other components of the Molecular Libraries and Imaging Initiative, and with interrelated activities in the public and private sector is shown in Figure 1, http://www.nimh.nih.gov/grants/rm04017fig1.pdf.

TECHNICAL ASSISTANCE WORKSHOP

NIH staff will conduct a technical assistance and information-sharing workshop in Bethesda, MD in May or early June of 2004. This workshop will allow potential applicants to discuss and clarify any issues or questions related to this RFA with NIH staff. The NIH is also seeking public comments regarding the potential use of a deviation to the standard patent rights clause to limit the rights of MLSCN center investigators to retain title to certain subject inventions involving the use of proprietary compounds in order to access and assemble the largest collection of compounds as possible for this project. The proposed deviated clause would provide title or exclusive rights to the provider of the proprietary compounds (see below). To accommodate individuals who cannot attend the meeting, the meeting will be webcast and made available for viewing on the Roadmap website. If you plan to attend the workshop, please contact Dr. Linda Brady (e-mail lbrady@mail.nih.gov or phone 301-443-5288) to register to attend. Potential applicants are encouraged to submit their questions to the email address listed above in advance of the meeting. Detailed information about the time and location of the meeting will be available on the NIH Molecular Libraries and Imaging Roadmap web page under Grants and Funding Opportunities (http://nihroadmap.nih.gov/molecularlibraries/grants.asp).

RESEARCH OBJECTIVES

The NIH wishes to facilitate the use of HTS approaches within the academic community to speed the discovery of molecular research tools (e.g., ligands, imaging probes, and new activities of existing drugs) in the public sector. It is anticipated that the MLSCN effort will catalyze scientific breakthroughs that will contribute to the identification of molecular entities or molecular classes that may have potential benefit for the development of therapeutics by the private sector. Through this approach, NIH wishes to stimulate research in the following areas: 1) discovery of novel biological targets that can inform studies of cell function and disease pathophysiology; 2) discovery, validation, and application of assays (screens) and disease models to evaluate the activity of novel small molecules; and 3) use of chemical genomic approaches to characterize the biology of genes of interest, cellular processes, and proteins associated with disease processes.

The public sector has not taken advantage of the considerable potential of HTS to improve the understanding of biology and disease mechanisms because access by academic scientists to automated screening facilities and diverse compound libraries is very limited. The NIH Molecular Libraries Initiative is intended to create and provide access to such resources and to facilitate the broad application of HTS in research in the public sector. The MLSCN effort differs from HTS efforts in private industry in several ways. First, because the NIH's interest is not limited to the identification of compounds with therapeutic effect, the range of the MLSCN effort is much broader. The MLSCN effort will screen small molecules in assays that encompass a broad range of novel biological targets and activities. If successful, the MLSCN will result in the identification, by the academic community, of a very large number of compounds for use as chemical probes to study many cellular pathways and the functions of major components of the cell in health and disease. Second, the biological screening data, assay protocols, and chemical structures for compounds tested in the MLSCN will be publicly available via the PubChem database, allowing data mining to obtain structural information about small molecules and the biological targets with which they interact. Third, the NIH Roadmap Initiative does not include plans to engage in the much more extensive aspects of drug development.

The MLSCN centers will vastly increase the ability of investigators in both the public and private sectors to use small molecules in basic biological research, and to translate the resulting findings into novel ligand discovery, and ultimately into therapeutics development in many disease areas through traditional routes of drug development. With respect to the latter, while drug development is not part of the Molecular Libraries and Imaging Initiative, individual Institutes and Centers at the NIH may, as they always have, subsequently decide to pursue certain drug development projects, particularly those that may not be attractive to the

private sector for economic reasons (e.g., the Spinal Muscular Atrophy Project, http://www.smaproject.org). The sharing of small molecules, assays, and screening data with the larger scientific community represents a new paradigm that promises to: facilitate the understanding of basic biological mechanisms; identify new biological targets and test them in disease models; and shorten the timeline for ligand and tool discovery. Potentially, the open sharing of these resources will also facilitate therapeutics development by the private sector with resulting benefits to public health, especially for rare or marginalized disorders.

The first phase of the MLSCN program is being implemented through this RFA as a 3-year pilot program that will support 6 or more pilot centers to develop sufficient capability, by the end of the three-year funding period, to screen a minimum of 100,000 compounds in 20 assays that have been adapted for HTS within each center per year. The NIH anticipates that this pilot program will lay the groundwork for a subsequent solicitation for a smaller number of fully operational HTS centers. Thus, the specific goal of this RFA is to support the establishment of a network of pilot Molecular Libraries Screening Centers that have or can develop the capabilities to: 1) implement a diverse array of both target-based and cell- or model organism-based phenotypic assays obtained from investigators in the public or private sector to HTS format; 2) screen a large number of compounds in the NIH Small Molecule Repository for biological activity in these assays; 3) provide synthetic chemistry to optimize screening hits into useful in vitro and/or in vivo biological probes; and 4) provide informatics support to track compounds, assays, and screening data. The MLSCN will make all biological screening data and assay protocols freely available to the public through the PubChem database.

In order to meet the goals and objectives of this Roadmap initiative, NIH is considering the use of a deviation to the standard patent rights clause in the Terms and Condition of Award. If a Determination of Exceptional Circumstances (DEC) were implemented herein, this clause deviation would serve to protect the pre-existing and future patent rights of suppliers of proprietary compounds for HTS in the MLSCN centers. The proposed clause deviation would be narrowly tailored to apply only to discoveries resulting from HTS of proprietary compounds, and would provide, for example, title or exclusive rights to new use inventions to the provider of the proprietary compounds, or otherwise dispose of the title and rights in a way that would encourage the provision of proprietary compounds to the centers. Furthermore, the MLSCN centers would have the right to ask for greater rights, as defined in the clause, if the supplier of the proprietary compound were not interested in the subject invention. The NIH is seeking public comments regarding the potential use of a deviation to the standard patent rights clause at the Technical Assistance Workshop; applicants are encouraged to submit their comments to lbrady@mail.nih.gov in advance of the meeting.

Note: Because the 3-year goal of screening 100,000 compounds in 20 assays may be an under- or over-estimate, this goal will be re-assessed annually by the MLSCN, the External Scientific Panel, and the NIH Project Team.

ORGANIZATIONAL STRUCTURE OF THE MLSCN

During the pilot phase, the MLSCN will be comprised of 6 or more extramural (academic and/or private sector) pilot centers and the NIH Chemical Genomics Center (NCGC, a screening center that is being established in the Intramural Research Program at NIH). The MLSCN will be established as a collaborative research network of centers with complementary abilities that will enable the network to address a wide range of biological opportunities.

It is envisioned that each center will bring to the MLSCN a specific set of expertise and skills in the areas of assay optimization, HTS, and synthetic chemistry to improve the biological utility of compounds identified as hits in biochemical, cell-based, and phenotypic assays. The focus of the MLSCN will be on implementing HTS-based assays for classes of proteins within different gene families and cell-based phenotypic assays rather than on specific human disorders or therapeutic areas. The rationale for this approach is that such a network will

be the best way of serving the diverse needs and interests of the many NIH Institutes and Centers that participate in the Roadmap Initiative. Each center within the MLSCN will be expected to include each of five critical functions:
(1)Assay Implementation, to optimize and automate target-based and cell-based phenotypic assays obtained from the scientific community for HTS, including the ability to obtain and produce cells, proteins, vectors, and other resources required;
(2) HTS, to screen appropriate/relevant set(s) of compounds, which are housed in the NIH Small Molecule Repository, in the optimized assays and to identify and confirms initial positive candidate compounds ("hits");
(3) Synthetic Chemistry and Probe Development, to apply rational strategies for the initial modification of candidate compounds to improve their ability to be used as in vitro and/or in vivo research tools, and to produce and screen second-generation libraries;
(4) Informatics, to address a number of different needs that the centers will have, including: automation and management of laboratory operations (e.g., compound tracking, control of robotic processes, data capture, and assay protocols) through a LIMS (laboratory information management system); procedures for data analysis/management and deposition of screening results and assay protocols to PubChem; and structure-activity analysis (SAR) of hits; and
(5) Administration and Management, to provide a structure for organization and integration of the required activities across the center, capabilities for key decision-making in the strategies employed for assay automation, screening, hits optimization and characterization, and establishment of efficient on-going operation of the center's screening activities.

NIH does not specify how these functions are to be organized. The applicant may choose to organize the proposed centers in terms of separate Cores or in any other manner deemed appropriate for the implementation of an effective pipeline. However, the application must clearly address how the proposed organization of the center will ensure that each of these functions is effectively accommodated.

Each of the functions is described in more detail below.

1. Assay Implementation. The goal of the MLSCN is to establish innovative biochemical, biophysical, and cell-based assays for biological targets or processes for which no highly specific and potent small molecule activator or inhibitor is broadly available to the public. However, the initial design and development of assays will not be the responsibility of the MLSCN centers. Rather, investigators in the broader scientific community will submit requests in response to an NIH Guide Notice that solicits biological assays to be optimized for HTS by the MLSCN, and those assay applications will be evaluated through a competitive process described below. The MLSCN centers will then be responsible for importing and adapting specific assays selected for implementation within the MLSCN.

The following list of target-based and phenotypic assays is intended to give a number of examples of assays that will potentially be of interest to the NIH, rather than to be exhaustive or prescriptive. Target-based assays may include those for G-protein coupled receptors (GPCRs), ion channels, transporters, orphan GPCRs, nuclear receptors, and kinases. Assays focusing on a broader range of functions could include those for macromolecular interactions using a variety of detection approaches such as mass spectrometry, nuclear magnetic resonance, or optical technologies, and molecular-level functional screens using enzymatic activity or reporter gene assays. Examples of non-traditional targets of interest include transcription factors, nucleic acids, multimeric proteins, membrane proteins, and polymorphic gene products, and subcellular processes such as molecular trafficking and translocation, post-transcriptional editing or splicing

of gene products, and protein or RNA stabilization. Phenotypic assays could include cellular processes (e.g., proliferation or apoptosis) or could utilize model organisms (e.g., yeast, worms, zebrafish, etc). Other assays of interest include those for metabolism, bioavailability, toxicity, blood-brain barrier permeability, or other phenomena that are not typically available in the academic community.

The proposed goal of the pilot centers will initially be to screen 10,000 compounds in 10 or more assays in the first year of the MLSCN program using 96- or 384-well plates, with an eventual goal of screening 100,000 or more compounds in a minimum of 20 assays in the third year. Applicants should clearly address a plan for adapting assays for HTS (e.g., assay miniaturization and automated processing) in order to achieve the proposed target goals for the first and third years (as indicated above), and discuss criteria for determining when an assay is sufficiently optimized to allow HTS at the anticipated scales of throughput.

It is desirable for each center to have an identifiable theme or concept around which it is initially organized (e.g., targets and detection approaches) and a plan to acquire the expertise and capability to import and optimize a broad range of biochemical or biophysical target-based assays and cell- or organism-based phenotypic assays during the three-year pilot phase. As indicated previously, the theme for a center should not be based on specific human diseases or therapeutic areas.

Applicants should describe the capabilities that they currently have or will develop to import a variety of assays from the scientific community and adapt them to a high throughput format. Issues such as experience with assay optimization, throughput, reproducibility, validation, cell culture, protein or vector production, and other relevant capabilities should be discussed.

2. HTS Implementation. A pilot center will need to be able to successfully carry out HTS using robotic technologies and high throughput imaging systems capable of detecting a variety of readouts (e.g., absorbance, fluorescence, luminescence, FRET, BRET, SPA, and biophysical readouts). Given the number of compounds to be screened, 96-, 384- and eventually 1536-well plate reader capabilities will be required. Centers will need to be able to validate HTS-based assay results, using for example Z' scores, unbiased statistical approaches, positive and negative controls, and ways to limit and identify false positives and false negatives. In most cases, confirmatory assays of hits, and at least one secondary screen (submitted by the referring investigator) will need to be run to identify true positives that would be candidates for further development as probes.

Applicants should justify each of the HTS component technologies proposed for inclusion in the pilot center in terms of how each one will be utilized as an integral component of the center's HTS capabilities. Applicants should also present a coordinated, viable plan for scaling up the HTS activities and, when appropriate, for implementing advances in detection, miniaturization, and robotics required for optimal high throughput implementation of assays to achieve the target capacity by the end of the pilot phase.

Synthetic Chemistry and Probe Development. It is essential that compounds identified as research tools for the investigation of particular targets and biological processes by the MLSCN are reliable and capable of providing reliable information on the activity of their intended targets. The probe compounds produced by the centers will need to be usable by the research community for in vitro and/or in vivo studies. In most cases, compounds identified by initial

screening ("hits") will not be ideal as research tools. It is likely that properties such as affinity, specificity, and solubility will need to be improved before a useful compound is obtained. Therefore, applicants should describe a plan for the development or acquisition of sufficient synthetic chemistry capability to generate a library of structurally related compounds (~100-300) around a confirmed hit and to test those compounds in the primary assay to identify derivatives with improved affinity, specificity, solubility, and bioavailability. Chemistry efforts could include optimization by structure-activity relationships (SAR) when a pharmacophore can be identified, including directed library synthesis and structure-guided design. The minimum characteristics that a probe compound will need to have to be a useful research tool will be determined by the MLSCN Steering Group and the NIH Project Team; it is anticipated that such characteristics will include <100 nM affinity, >100-fold selectivity against related targets, and solubility in aqueous solutions or in a low concentration of DMSO. NIH recognizes that whatever the characteristics of the probes, further modification will be necessary to produce compounds that are useful for in vivo studies. For this reason, all probes, as well as the data and hits from which they are derived, will be made available to all researchers. Support for such projects will be through Roadmap-related Program Announcements or other NIH funding mechanisms.

4. Informatics. Adequate informatics capabilities will be critical to multiple components of the center. Automation, sample tracking, laboratory procedures, quality control, data management, deposition of screening data, assay protocols, and other relevant information to PubChem, and data analysis all depend on sufficient informatics capabilities and resources.

Applicants should present a clear set of operational plans for ensuring that the informatics needs of the center are addressed, including the issue of integration to the extent that it contributes to the efficiency of the center's operation. Issues that should be addressed include plans for acquisition and analysis of primary screening data, and data generated from screening of a second-generation library of structurally related compounds generated around a confirmed hit. Applicants should describe their capabilities or plans to acquire resources for computational chemistry, pharmacophore modeling, and SAR analysis of new leads (e.g., QSAR, CoMFA, Sybil software).

In preparing the informatics plan, the applicant should take into account that once the MLSCN is established, the MLSCN Steering Group will address issues of possible standardization of operating procedures across centers such as quality control and quality assessment for assay and screening procedures, and data deposition practices for submission of screening data, assay protocols, and other information to PubChem. Although the proposed informatics plan will be evaluated for adequacy by the review committee, once the centers network is established, the MLSCN Steering Group will identify opportunities and develop guidelines for increasing the inter-operability of the centers. Applicants will be expected to have a high degree of flexibility and be willing to adopt uniform policies and procedures recommended by the MLSCN Steering Group.

All screening data and descriptions/protocols for assays optimized for HTS by the MLSCN are required to be deposited immediately in the public domain (via PubChem) after they have been certified for accuracy. The procedures for the deposition of screening data and assay protocols to PubChem will be coordinated directly with the National Center for Biotechnology Information (NCBI), the lead on the PubChem initiative. PubChem staff at NCBI will suggest specific formats for data deposition and will work with MLSCN centers as necessary to ensure accurate transmission. For chemical structure data, it is anticipated that PubChem will support, among others, existing formats such as SDF or MOL files. For screening assay descriptions and results, it is anticipated that PubChem will support depositions based on best current technologies including XML exchange specifications. For chemical synthesis descriptions of small molecules in the Repository, PubChem will support deposition of text descriptions and citations.

5. Administration and Management. The management of a MLSCN center will require a well-conceived and implemented management plan and a significant commitment by the

PI of the project. The PI of an MLSCN center funded under this RFA is expected to devote at least 25% effort to the project. The application should describe the management plan for the proposed center, and how the plan will support its proposed goals. It should describe the organization of the proposed center and its management structure and should address the integration of the functional components to form an efficient assay optimization, screening, and hits optimization chemistry pipeline for generating small molecule research tools. The plan should specifically address interactions between key personnel and reporting relationships. Recruitment and training of personnel should be discussed. The plan should specifically address how any collaborations or subcontracts will be managed.

The management plan should also address the interactions of the proposed center with the other components of the MLSCN Network (e.g., the Small Molecule Repository, the MLSCN Steering Group, the Coordinating Center, and the NIH Project Team; these components are described in more detail below in the Definitions section). The PI is strongly encouraged to consider proposing a project manager for the center. It is also expected that each MLSCN center will have a Center Steering Committee (CSC) that includes key center personnel, external advisors, and an NIH Science Officer (defined below). The CSC should meet at least on an annual basis to review progress and provide advice on strategies for assay automation, screening, hits optimization and characterization. Plans for organizing a CSC should be described in the application, but potential members of the CSC should not be contacted until after an award has been made, and the names of potential members should not be listed in the application.

Note: Because of the complexity of the MLSCN, program staff from NIH expect to visit each MLSCN center periodically to conduct an administrative site visit. U54 centers should be prepared for annual visits and should budget appropriately (including travel for collaborators and other necessary costs).

In addition to the functions described above, there are a number of other issues important to the successful operation of the MLSCN that should be addressed separately in the application:

1. Governance Structure of the MLSCN. The Molecular Libraries and Imaging Initiative consists of multiple interacting components, many of which contribute activities that are directly related to the successful operation of the MLSCN centers. The coordination of these separately funded activities is one of the primary reasons why the NIH will fund the MLSCN using the cooperative centers (U54) mechanism. To facilitate the coordination, the NIH Project Team proposes the following governance structure for the MLSCN and related Molecular Libraries and Imaging Initiative activities. For additional details, see the Definitions section in the RFA, and Figure 2, http://www.nimh.nih.gov/grants/rm04017fig2.pdf.

o Each MLSCN center will have an individual CSC as described above.

o The MLSCN Steering Group will consist of the PIs for each center within the MLSCN network, including the NCGC center located in the Intramural Research Program at NIH, and the NIH Science Officers. The PI of the Small Molecule Repository, the PI of the Coordinating Center, and a representative from PubChem will be ex officio members. The MLSCN Steering Group will be responsible for the overall coordination of the screening center network, and the group through which the centers will interact with the NIH Project Team and other components of the Roadmap Initiative. It will develop criteria and implement procedures for data quality assessment, consider standard operating procedures across centers, and develop and recommend policies for data release (e.g., the exchange of screening data, assay protocols, and other materials with the wider scientific community) for concurrence by the NIH Project Team. The MLSCN Steering Group will develop a plan for assignment of assays to specific centers within the network after considering the evaluation of assay proposals by the MLSCN Assay Access Committee (see definitions below); the Steering Group will then recommend the assay distribution plan to the NIH Project Team for concurrence. The MLSCN Steering Group will consider each center's

proposed strategy for optimization of candidate compounds ("hits"). In the event that the number of candidate compounds identified by a specific center exceeds its capacity for chemical optimization, the MLSCN Steering Group will develop a plan for re-distribution of probe development within the network and will recommend the plan to the NIH Project Team for concurrence.

o The Coordinating Center will provide a range of important services to the MLSCN. The Coordinating Center will assist in coordinating and tracking the activities of the MLSCN and its component screening centers, and will maintain a website that will provide up-to-date information on assays accepted for implementation in specific MLSCN centers, compounds accepted for entry into the Small Molecule Repository, confirmed hits within the network, and data depositions to PubChem. The Coordinating Center will also provide administrative support to the MLSCN Assay Access Committee, which will evaluate proposals from the research community for assays to be implemented by the MLSCN, and to the MLSCN Compound Acquisition Committee, which will evaluate requests for compounds to be incorporated into the Repository. The Coordinating Center will be implemented as a contract with a Request for Proposals (to be issued shortly).

o The NIH Project Team will be composed of NIH staff who are actively involved in the management and implementation of this Roadmap Initiative. The Project Team will be the operational governing body for the network that reviews and, upon concurrence, implements the guidelines and policies recommended by the MLSCN Steering Group, and will act as a second-level of review for the distribution of assays to each of the screening centers and the acquisition of compounds for the Small Molecule Repository.

o The Molecular Libraries and Imaging Implementation Group (MLIIG) will be composed of the Directors of NHGRI, NIMH, and NIBIB and the lead NIH staff for each of the components of the Roadmap Initiatives. The MLIIG will provide overall guidance for all components of this Roadmap Initiative.

2. Acquisition of Assays. The function of the MLSCN centers will be to receive assays that have been developed by members of the scientific community, adapt them for high-throughput implementation, and use them to screen the compound collection provided by the NIH Small Molecule Repository to identify and confirm compounds that have the desired effect in the assay. Proposals for innovative assays for screening center implementation will be solicited from the scientific community through notices in the NIH Guide and in scientific journals. Applications will be reviewed for scientific merit, including suitability for high-throughput implementation, by an MLSCN Assay Access Committee convened by NIH. The results of the reviews and information about available capacity at each center will form the basis for assay prioritization and assignment decisions. The information will be provided on a regular basis to the MLSCN Steering Group, which will make recommendations about assay assignments. The NIH Project Team will provide a second level of review of the decisions of the Steering Group and give final approval for assay assignments on a time frame suitable to the screening capacity and expertise of the centers. Applicants for this MLSCN RFA-RM-04-017 should assume, therefore, a continuous and regular supply of new assays for implementation, and do not need to address assay acquisition in their applications. The applications should address the issue of evaluating and adapting assays for high-throughput implementation and should present a clear plan for doing so.

The MLSCN centers will not have a privileged position relative to the rest of the scientific community with respect to access to HTS services. Should the PI or any other participant in an MLSCN center wish to implement an assay of their own devising, they will have to submit that assay for review and prioritization according to the process described in the previous paragraph. Should such an assay be placed on the priority list, the NIH Project Team will take the PI's interest into account in assigning that assay to the requesting center.

3. Data Release. The MLSCN will function opening by making all data available to

the scientific community. It is expected that MLSCN centers will immediately release data (i.e., screening data and assay descriptions) to PubChem as soon as the data have been determined to be reliable. It is anticipated that the MLSCN Steering Group will develop guidelines for standardizing the reliability/validation of screening data for different types of assays across centers. Responses to this RFA should include a statement of willingness to abide by the immediate data release policy for submission of screening data to PubChem.

o MLSCN members will submit data to PubChem in the format specified by NCBI, the lead on the PubChem initiative. PubChem staff at NCBI will suggest specific formats for data deposition and will work with MLSCN centers as necessary to ensure accurate transmission. For chemical structure data, it is anticipated that PubChem will support, among others, existing formats such as SDF or MOL files. For screening assay descriptions and results, it is anticipated that PubChem will support depositions based on best current technologies including XML exchange specifications. For chemical synthesis descriptions of small molecules in the Repository, PubChem will support deposition of text descriptions and citations.
o Upon submission to PubChem, all data will be made freely available to the entire research community in a form that would allow for redisplay and reanalysis, so that maximal utility of this research resource will be realized. It is NIH's expectation that users of these data will respect the legitimate interests of the producers to analyze and publish their results by treating the data as unpublished information, until otherwise indicated. As with any unpublished data, it is expected that users will provide proper citation of the source of the data.
o The individual investigators within the MLSCN may publish the results of their own screening efforts. Neither these individual publications nor any MLSCN network publications should delay the other's publications.
o The MLSCN network may publish global analyses of the results of the screening effort. The MLSCN Steering Group, with guidance from the External Scientific Panel and the NIH Project Team, will establish a timeframe once the MLSCN has been launched and there is a better understanding of the timeframe and scope of the project.
o MLSCN members will fully disclose algorithms, software source code, and experimental methods to the other members of the network for purposes of scientific evaluation and will be strongly encouraged to make them available to the broad research community.

4. Cost Sharing. Cost sharing by applicant institutions is not a requirement of this RFA. NIH is aware that potential applicants will be in different stages of their development of a Molecular Libraries Screening Center. Indeed, one of the reasons that the MLSCN is being initiated as a pilot center phase is to provide interested investigators and institutions with the opportunity to get involved in HTS screening. At the same time, NIH is aware that a number of institutions have already established such activities and have already committed institutional funds to them. Cost sharing will not be a review criterion; any comments that reviewers might make will be reported in an administrative note for consideration by program staff.

In summary, the minimal features of a center within the MLSCN are:

o A specific set of expertise and skills in molecular screening.
o A capacity to implement innovative cell-based biochemical, biophysical, and functional assays for biological targets and cell- or model organism-based phenotypic assays.
o A plan with explicit milestones and timelines for achieving the three-year goal of an annual capacity to screen 100,000 compounds in 20 different assays.
o An ability to adapt and modify HTS approaches, HTS-based assay protocols, optimization chemistry, and computational chemistry as the technology and demands

on the center change.
o A capability to provide sufficient informatics to support LIMS, compound tracking, data analysis, data handling, and data deposition to PubChem.
o A statement of the proposed center's willingness to abide by the immediate data release requirement for submitting screening data to PubChem.
o A sharing plan for access to any research resources generated by the proposed centers.
o A plan for addressing if and how the proposed center will exercise intellectual property rights, should any intellectual property be generated under a center award, while making such research resources available to the broader scientific community in accordance with the goals of the Roadmap Initiative.
o A technology development capability that will facilitate the integration of technology improvements (e.g., robotics, assay miniaturization, chemistry, and protocols) to increase the efficiency and decrease the cost of the center's screening capacity.
o A plan for center management addressing how the functional units will be integrated and how key personnel will interact.
o A plan for implementing adequate quality control procedures including the reproducibility of assay data, and carrying out effective quality assessment.
o A high degree of flexibility and ability to interact with other centers within the MLSCN, the Coordinating Center, the Small Molecule Repository, PubChem, the NIH Project Team and the proposed governance for the MLSCN, and with other entities with whom it may be necessary to interact in order to make a maximum contribution to the Roadmap Initiative.

MECHANISM OF SUPPORT

This RFA will use the NIH U54 award mechanism. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. The anticipated award date is March 2005.

The U54 is a cooperative agreement award mechanism. In the cooperative agreement mechanism, the Principal Investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantially involved as a partner with the Principal Investigator, as described under the section "Cooperative Agreement Terms and Conditions of Award".

This RFA uses just-in-time concepts. It also uses the non-modular budgeting format. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

The NIH intends to issue a subsequent RFA to establish a MLSCN of three to five larger-scale, fully operational centers with state-of-the art capabilities and with a higher level of throughput than specified as the third-year goal of the pilot MLSCN program (i.e., an annual capacity to screen 100,000 compounds in 20 different assays optimized for HTS within the center per year). This future RFA will allow funded pilot centers to apply for a competitive renewal award and will likely allow applications from potential new centers. The initial period of support for a U54 center under the current RFA is expected to be three years.

FUNDS AVAILABLE

The NIH intends to commit approximately $20 million in FY2005 to fund approximately 6 or more new awards in response to this RFA. An applicant should request a project period of 3 years. The budget (direct costs, excluding equipment) may not exceed $1,000,000 in the first year, $2,000,000 in the second year, or $3,000,000

in the third year. The F&A costs (sometimes known as indirect costs) of subcontractors will not count against these dollar limits. Costs for equipment may be included in year one, up to $500,000; these costs will not count against the $1,000,000 direct cost limit, but should be well justified. No limit is placed on the allowable costs for equipment in the second and third years. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size of each award will also vary. Although the financial plans of the NIH provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic institutions/organizations
o Foreign institutions are not eligible to apply for an MLSCN center but can participate as a subcontract within a center.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

DEFINITIONS

COORDINATING CENTER. A Coordinating Center will be established by NIH through a contract, and will provide a range of important services to the MLSCN. The Coordinating Center will assist in coordinating and tracking the activities of the MLSCN and its component screening centers, and will maintain a website that will provide up-to-date information on assays accepted for implementation in specific MLSCN centers, compounds accepted for entry into the Repository, confirmed hits within the network, and data depositions to PubChem. The Coordinating Center will also provide administrative support to the MLSCN Assay Access Committee, which will evaluate proposals from the research community for assays to be implemented by the MLSCN, and to the MLSCN Compound Acquisition Committee, which will evaluate requests for compounds to be incorporated into the Small Molecule Repository.

EXTERNAL SCIENTIFIC PANEL. The External Scientific Panel will be composed of 6-8 senior non-federal advisors who are not directly involved in the activities of the MLSCN and who will be appointed by the NIH Project Team with concurrence from the MLIIG. The External Scientific Panel will collectively provide expertise in molecular screening and the needs of academic scientists who will utilize the resources generated by the MLSCN, and will review the overall MLSCN program on a regular basis and provide feedback and recommendations to the NIH Project Team and the MLIIG.

MLSCN ASSAY ACCESS COMMITTEE. An NIH committee that will evaluate assay proposals for scientific merit and feasibility. The Scientific Review Administrator (SRA) for this panel will be an NIH review staff member and the panel members will be primarily non-federal scientists approved by the NIH Project Team. Recommendations of the MLSCN Assay Access Committee will be communicated to the NIH Project Team and to the MLSCN Steering Group.

MLSCN COMPOUND ACQUISITION COMMITTEE. An NIH committee that will evaluate

proposals for the acquisition of small molecules from public and private sources for the Small Molecule Repository. The SRA for this panel will be an NIH review staff member and the panel members will be approved by the NIH Project Team. Recommendations of the MLSCN Compound Acquisition Committee will be communicated to the NIH Project Team and to the MLSCN Steering Group.

MOLECULAR LIBRARIES AND IMAGING IMPLEMENTATION GROUP (MLIIG). An oversight group
composed of the Directors of NHGRI, NIMH, and NIBIB, who are the chairs for the Molecular Libraries and Imaging Roadmap Initiative, and the lead NIH staff for each component of the Roadmap. The group will provide overall guidance for the MLSCN program, coordination with other components of the Initiative, and resolution for cases in which consensus cannot be reached by the MLSCN Steering Group and the NIH Project Team. NIH Science Officers will not be voting members of the NIH Project Team or the MLIIG.

MLSCN STEERING GROUP. The Steering Group for the overall MLSCN consisting of the Director (PI) of each of the extramural screening centers, the PI of the NIH Chemical Genomics Center (NCGC, the center housed in the NIH Intramural Research Program), and the NIH Science Officer for each extramural center (defined below). The NIH Science Officers may vote, and their total votes will count 1/2 as much as the total votes of the MLSCN center PIs. The PI of the of the Small Molecule Repository, the PI of the Coordinating Center, and the designated lead for PubChem will be ex officio members. The Steering Group will be the primary operational governing board of the MLSCN. The functions of this group include: 1) recommending the assignment and scheduling of assays and tasks in conjunction with the NIH Project Team; 2) developing guidelines to standardize the validation of screening data in different types of assays across centers; 3) developing uniform procedures and policies for assay validation, data quality measures, assessment procedures, and annotation conventions for data depositions in conjunction with the NIH Project Team and NCBI PubChem designee; 4) serving as a venue for coordination on improving the state-of-the-art HTS in the academic sector by reporting progress, disseminating best practices, and collectively evaluating new procedures, resources, and technologies; 5) monitoring, developing, and implementing quality control procedures that assure consistency across centers; 6) facilitating the timely release of data in the format and on the schedule recommended by the MLSCN Steering Group and implemented by the NIH Project Team; and 7) developing and recommending progress report formats for both individual centers and for the MLSCN Program as a whole to the NIH Project Team.

NIH PROJECT TEAM. The NIH Project Team will serve as the governing body that coordinates and oversees the interaction of NIH with the centers and the MLSCN Steering Group. The NIH Project Team is composed of representatives from each of the NIH Institutes and Centers participating in the Molecular Libraries Initiative and will be overseen by the MLIIG. The functions of the NIH Project Team include: 1) setting guidelines and policies for the MLSCN based on recommendations from the MLSCN Steering Group; 2) nominating a rotating chair to communicate policy information to the MLSCN Steering Group and Coordinating Center; 3) providing the second level of review of the recommendations of the Assay Review Panel and the Compound Review Panel; 4) overseeing the assignment of assays to specific centers within the MLSCN; 5) overseeing the addition of new compounds to the Small Molecule Repository; and 6) communicating information about the progress of each center and the functions of the MLSCN Steering Group to the External Scientific Panel. NIH Science Officers will not be voting members of the NIH Project Team or the MLIIG.

PUBCHEM. The NCBI database for the deposition of primary and secondary screening data for compounds in the Small Molecule Repository that are tested in assays optimized for HTS in the MLSCN, accession numbers for compounds in the NIH repository, description of the assays and assay protocols implemented at each center, depositor-supplied references to synthesis and/or isolation protocols for the compounds, depositor-supplied references to sources and/or suppliers, and

computationally derived Lipinski parameters, if available. LinkOuts may be established to capture additional biological data obtained in follow-up screening carried out in the public or private sector (see http://www.ncbi.nlm.nih.gov/entrez/linkout/).

SCREENING CENTER STEERING COMMITTEES (CSC). The Steering Committee for each individual screening center (intramural and extramural centers) consisting of key center personnel, external advisors, and the NIH Science Officer.

SPECIAL REQUIREMENTS

A. Public Domain of Data

The overall goal of the MLSCN program is to make biological screening data, compounds, and assays readily available and accessible to the scientific community for use in research. Restricted availability of unique research resources, upon which further studies are dependent, can impede the advancement of research. The NIH is interested in ensuring that the research resources developed through this funding agreement become readily available to the broader research community in a timely manner for further research, development, and application, in the expectation that this will lead to products and knowledge of benefit to the public health. It is expected that resources to be shared will include, among others, the screening data, assay protocols, and materials.

To address the interests of the government in the availability of, and access to, the results of publicly funded research, NIH requires applicants who respond to this RFA to propose detailed plans for sharing the research resources generated through the grant. It is expected that the resources to be shared include all materials (e.g., screening data, and assay protocols) developed in projects funded under the RFA. The investigator's intent to make screening data available immediately for deposition in PubChem, after certification for accuracy, should also be specified in the application and will be considered during the review of the plan for sharing.

The NIH proposes the following for applicants to consider for sharing data and research resources:

1. HTS of non-proprietary compounds in the Small Molecule Repository. Compounds identified as "hits" (initial positive candidate compounds) may not be considered to be patentable because they would not likely be immediately useful as research tools or a final product. These screening data should be made available immediately for deposition in PubChem, after certification for accuracy. However, under exceptional circumstances, if a non-proprietary compound were well-enough developed to support the filing of a use invention, a waiver of the requirement for immediate deposition of screening data would be considered by the NIH Project Team and the MLSCN Steering Group. In such cases, a 60-day (calendar days) delay for the deposition of the select screening data to PubChem by the MLSCN may be acceptable to allow the MLSCN center applicant to file a patent on specific compounds.

2. Synthetic chemistry and probe development. The generation of secondary libraries around a confirmed, non-proprietary hit is likely to result in compounds with enhanced affinity, specificity, and solubility in the target assay. Some of these novel compounds may be valuable leads for further commercial development. In such cases, and under exceptional circumstances, a 60-day (calendar days) delay for the deposition of the select screening data to PubChem by the MLSCN may be acceptable to allow the MLSCN center applicant to file a patent on specific compounds if desired.

3. Assay implementation. Optimization of assays for HTS by the MLSCN centers may require close interaction with the investigator who originally developed the assay. In such cases, it should be recognized that co-inventorship of improved assay inventions may result, dependent

on the inventive contributions of the parties involved. In cases where a patent would be filed for an assay, the requirement for immediate deposition of screening data and assay description would be reconsidered by the NIH Project Team and MLSCN Steering Group on a case-by-case basis, again under exceptional circumstances. In such cases, a 60-day delay (calendar days) for the deposition of the select screening data to PubChem by the MLSCN may be acceptable to allow the MLSCN center applicant to file a patent on specific compounds.

The investigator should also include a sharing plan for access to any other research resources (e.g., HTS methods, development of technology to automate and/or miniaturize assays for HTS, data analysis software, etc.) that are expected to be generated by the proposed centers. It is important that research resources and materials be made readily available to investigators in the scientific community for research purposes. Research resources and materials may also be made available to investigators for commercial purposes with appropriate restrictions and licensing terms as the applicant and their institution deem necessary. The plans for the development of resources for use by the biomedical community should have the appropriate timeliness and mileposts. In the development of the sharing and intellectual property plans, applicants should confer with their own institution's office(s) responsible for handling technology transfer related matters and/or their sponsored research office. If applicants or their representatives require additional guidance in preparing these plans, they are encouraged to make further inquiries to the program contact listed below for such matters.

All awards made under this RFA are subject to the Final NIH Statement on Sharing Research Data (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html) and the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources (http://ott.od.nih.gov/NewPages/RTguide_final.html).

The scientific review group will evaluate the adequacy of the proposed plan for sharing and data access. Comments on the plan and any concerns will be presented in an administrative note in the Summary Statement. These comments will not affect the priority score of the application. The adequacy of the plan will be considered by NIH program staff and will be a factor in determining whether the cooperative agreement shall be awarded. The sharing plan approved by program staff, after negotiation with the applicant when necessary, will become part of the terms and conditions of the award. NIH program staff will evaluate the compliance with the sharing plan and scientific progress in the non-competing continuation application; such compliance will be a criterion for continued funding of the award.

B. Intellectual Property Rights and Accessibility of Research Resources

NIH is interested in ensuring that the research resources developed through this RFA become readily available to the research community. NIH will convene a meeting in May/June 2004 to further discuss intellectual property issues associated with the Molecular Libraries and Imaging Probes Roadmap Initiative. Subsequent to that meeting, NIH will develop a set of intellectual property guidelines for the Initiative, and will post these guidelines in the NIH Guide prior to the receipt date for this RFA. Applicants are expected to comply with the intellectual property guidelines adopted by NIH for the MLSCN RFA.

Applicants who respond to this RFA should include a plan addressing if, or how, they will exercise their intellectual property rights, should any intellectual property be generated under a center award, while making such research resources available to the broader scientific community for research purposes consistent with the goals of the NIH Molecular Libraries and Imaging Initiative. It is important that research resources and materials be made readily available to qualified investigators in the scientific community for research purposes. A reasonable time frame for release of materials should be specified in the sharing plan and will be considered during the review. Furthermore, transfers of research resources must be made consistent with the

NIH Research Tools Policy (http://ott.od.nih.gov/NewPages/RTguide_final.html) and other NIH sharing policies. In the development of the sharing and intellectual property plans, applicants should confer with their own institution's office(s) responsible for handling technology transfer related matters and/or their sponsored research office. If applicants or their representatives require additional guidance in preparing these plans, they are encouraged to make further inquiries to the appropriate contacts listed below for such matters.

As described previously, the NIH will be seeking public comments regarding intellectual property issues at the Technical Assistance Workshop. Potential applicants and other interested parties are invited to present comments as well as provide alternative approaches that would serve to meet the objectives/goals of this Initiative without the use of the deviation. All comments will be considered and discussed at the meeting. Intellectual property issues will also be discussed at a separate NIH meeting to be held in May/June. Both meetings will be used to guide NIH policy for the MLSCN centers. If a Determination of Exceptional Circumstances (DEC) were implemented, this clause deviation would serve to protect the pre-existing and future patent rights of suppliers of proprietary compounds for HTS in the MLSCN centers. If used, the proposed clause deviation would be narrowly tailored to apply only to discoveries resulting from HTS of proprietary compounds, and would provide, for example, title or exclusive rights to new use inventions to the provider of the proprietary compounds, or otherwise dispose of the title and rights in a way that would encourage the provision of proprietary compounds to the centers. Furthermore, the MLSCN centers would have the right to request greater rights if the supplier of the proprietary compound is not interested in the subject invention.

The scientific review group will evaluate the adequacy of the proposed plan for handling intellectual property rights. Comments on the plan and any concerns will be presented in an administrative note in the Summary Statement. These comments will not affect the priority score of the application. NIH program staff, in determining whether the application shall be awarded, will consider the adequacy of the proposed plan. The plan as approved, after negotiation with the applicant when necessary, will be part of the terms and conditions of the award. Evaluation of non-competing continuation applications will include assessment of the center awardee's adherence to the proposed plan, and will be a criterion for continued funding of the award.

Applicants also are reminded that the grantee institution is required to disclose each subject invention to NIH within two months after the inventor discloses it in writing to grantee institutional personnel responsible for patent matters. The awarding Institute reserves the right to monitor awardee activity in this area to ascertain if patents or patent applications on automation of biological assays, genetically encoded reporters, cell lines, and vectors used in HTS-based assays, or other patentable subject matter are adversely affecting the goals of this RFA.

Principles and guidelines for recipients of NIH research awards on obtaining and disseminating biomedical research resources can be found at http://ott.od.nih.gov/NewPages/RTguide_final.html. This document also defines terms, parties, responsibilities, prescribes the order of disposition of rights, prescribes a chronology of reporting requirements, and delineates the basis for and extent of government actions to retain rights. Patent rights clauses may be found at 37 CFR Part 401.14 and are accessible from the Interagency Edison web page, http://www.iedison.gov.

COOPERATIVE AGREEMENT TERMS AND CONDITIONS OF AWARD

As part of the U54 Specialized Center Grant process, the following Terms and Conditions of Award and details of the arbitration procedures pertaining to the scope and nature of the interaction between the NIH staff and the participating awardees will be incorporated into the Notice of Grant Award and provided to the Principal Investigator and the institutional official at the time of award. These procedures will be in addition to the customary programmatic and financial negotiations that occur in the administration of grants.

Cooperative agreements are assistance mechanisms subject to the same administrative requirements as grants. The special Terms and Conditions of Award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR Part 74 and 92, and other HHS, PHS, and NIH grant administration policies and procedures. Cooperative Agreements are subject to the administrative requirements outlined in pertinent OMB, HHS, PHS, and NIH guidelines, with particular emphasis on HHS regulations at 42 CFR Part 52 and 45 CFR Part 74. Facilities and Administrative Cost (indirect cost) award procedures will apply to cooperative agreement awards in the same manner as for grants.

The administrative and funding instrument used for this program is a Cooperative Agreement (U54), an "assistance" mechanism (rather than an "acquisition" mechanism) in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardees and NIH Science Officers (defined below).

Failure of the awardees to meet the performance requirements, including these special terms and conditions of award, or significant changes in level of performance, may result in a reduction of budget, withholding of support, suspension and/or termination of the awards.

1. Awardee Rights and Responsibilities

The PI will coordinate project activities scientifically and administratively at the awardee institution. The PI will have primary responsibility for defining the details for the projects within the guidelines of this RFA RM-04-017, and for performing all scientific activities. The PI will agree to accept the close coordination, cooperation, and participation of the NIH Science Officer(s), the NIH Project Team, the MLSCN Steering Group, the Molecular Libraries Coordinating Center, and Molecular Libraries External Scientific Panel in those aspects of scientific and technical management of the project as described below. Specifically, the PI will:

o Determine experimental approaches, design protocols, set project milestones, and conduct experiments.
o Propose protocol modifications as required.
o Analyze and interpret research data.
o Provide goals for assay optimization, screening throughput, quality, and cost to the NIH Science Officer and/or Program Officer as requested, usually at the outset of the award and in six-month progress reports, but also at other times if requested.
o Release data according to the approved plans for timely sharing of research resources and data generated through the award, and publish results, as agreed upon by the MLSCN Steering Group and the NIH Project Team.
o Ensure that primary and secondary screening data and assay protocols are deposited in a centralized database, PubChem, according to the timeline implemented by the NIH Project Team.
o Establish a Center Steering Committee (CSC) consisting of key center personnel, external scientific advisors, and the NIH Science Officer, and prepare a concise summary of their meeting within 30 days.
o Serve on the MLSCN Steering Group.
o Provide information to the NIH Program Officer concerning progress, by submitting periodic progress reports in a standard format, as agreed upon by MLSCN Steering Group.
o Accept and implement all scientific, practical, and policy decisions approved by the MLSCN Steering Group and the NIH Project Team.
o Share with other MLSCN facilities research resources, tools, and data of interest

to those facilities, as directed by the MLSCN Steering Group and agreed upon by the NIH Project Team.
o Participate, along with critical staff, in the MLSCN Steering Group meetings held twice annually in the metropolitan Washington, DC area.
o Be prepared for annual administrative site visits by NIH staff

Note: The NIH Intramural Research Program's NIH Chemical Genomics Center (NCGC) will participate with the same rights and responsibilities, and within the same governing structure, as the extramural awardees.

2. Coordinating Center

A Coordinating Center will be established by NIH as a contract, and will provide a range of important services to the MLSCN. The Coordinating Center will assist in coordinating and tracking the activities of the MLSCN and its component screening centers, and will maintain a website that will provide up-to-date information on assays accepted for implementation in specific MLSCN centers, compounds accepted for entry into the Repository, confirmed hits within the network, and data depositions to PubChem. The Coordinating Center will also provide administrative support to the MLSCN Assay Access Committee, which will evaluate proposals from the research community for assays to be implemented by the MLSCN, and to the MLSCN Compound Acquisition Committee, which will evaluate requests for compounds to be incorporated into the Small Molecule Repository.

3. NIH Science Officers

The NIH Science Officers will be NIH program staff who will have substantial scientific involvement during the conduct of this activity, through technical assistance, advice, and coordination above and beyond normal program stewardship for grants. This includes functioning as a peer with the PIs, facilitating the partnership relationship between NIH and the facilities funded under this RFA, helping to maintain the overall scientific balance in the program commensurate with new research and emerging research opportunities, and ensuring that the activities of the MLSCN centers are consistent with the mission of the NIH Molecular Libraries and Imaging Initiative. Each MLSCN center will have a designated NIH Science Officer, and a given individual may be the NIH Science Officer for more than one center. The NIH Science Officers will be selected by the NIH Project Team.

The NIH Science Officers will:

o Provide relevant scientific expertise and overall knowledge.
o Assist in avoiding unwarranted duplication of effort across centers, and help coordinate collaborative research efforts that involve multiple centers.
o Review and comment on critical stages in the research program before subsequent stages are implemented.
o Assist in the interaction between the awardee and investigators at other institutions.
o Provide information about ongoing NIH-supported research and resources.
o Attend Center Steering Committee (CSC) meetings as a voting member, and assist in developing operating guidelines, quality control procedures, and consistent policies for dealing with recurrent situations that require coordinated action in conjunction with the MLSCN and the NIH Coordinating Center.
o Attend the MLSCN Steering Group meetings as a voting member, and assist in the group process of setting research priorities and milestones, deciding optimal research approaches and protocol designs, and contributing to the adjustment of research protocols or approaches as warranted. The Science Officer will assist and facilitate the group process and not direct it.
o Serve as scientific liaison between the awardees, other NIH program staff, and

the NIH Project Team.
o Assist in developing timelines for the wide distribution of screening data to the scientific community.
o Retain the option to recommend additional research endeavors within the constraints of the approved research and negotiated budget.
o Retain the option to recommend re-allocation of NIH support among awardees, as scientific goals evolve.
o To help carry out these duties, Science Officers may consult with non-NIH experts in the field.

4. NIH Program Officer:

The awarding Institute will appoint a Program Officer who will have responsibility for normal program oversight and stewardship of the MLSCN centers. The Program Officer may also serve as the designated Science Officer.

The NIH Program Officer will:

o Exercise the normal stewardship responsibilities of an NIH Program Officer.
o Carry out continuous review of all activities to ensure objectives are being met.
o Attend CSC meetings as a non-voting participant, if not also participating as a Science Officer.
o Attend the MLSCN Steering Group meetings as a non-voting participant, if not also participating as a Science Officer.
o Have the option to recommend, with the advice of the External Scientific Panel, the withholding or reduction of support from any center that substantially fails to achieve its goals according to the milestones agreed to at the time of the award, fails to maintain state-of-the-art capabilities, or fails to comply with the Terms and Conditions of the award.

5. NIH Project Team Responsibilities

The NIH Project Team will serve as the governing body that coordinates and oversees the interaction of NIH with the MLSCN centers and the MLSCN Steering Group. The Project Team membership will include representatives from each of the NIH Institutes and Centers participating in the Molecular Libraries and Imaging Initiative or their designated representative. Science Officers will be ex officio (non-voting) members of the NIH Project Team. The Project Team will receive recommendations from the MLSCN Steering Group and will be overseen by the MLIIG.

The NIH Project Team will:

o Set guidelines and policies for the MLSCN based on recommendations from the MLSCN Steering Group.
o Nominate a rotating chair to communicate policy information to the MLSCN Steering Group, Coordinating Center, Small Molecule Repository, and PubChem.
o Review recommendations of the MLSCN Steering Group for the distribution of assays to each of the centers within the MLSCN and make final assignments of individual assays to specific centers on a timetable that will ensure efficient operation of the Network.
o Oversee the addition of new compounds to the Small Molecule Repository.
o Communicate information about the progress of each center, the MLSCN program, and other components of the Molecular Libraries and Imaging Initiative, as well as activities of the MLSCN Steering Group, to the External Scientific Panel.

6. Collaborative Responsibilities: MLSCN Steering Group Functions

The MLSCN Steering Group is the operational governing board responsible for overall coordination of the MLSCN program, and the committee through which the NIH Project Team interacts and collaborates with the individual screening centers. The MLSCN Steering Group membership will include the PI of each of the extramural centers and the NCGC (the NIH intramural center) and the NIH Science Officers. The PIs of the Small Molecule Repository, Coordinating Center, and PubChem will be ex officio (non-voting) members. The MLSCN Steering Group will coordinate the activities of the centers and the dissemination of screening data, assay protocols, and other materials with the wider scientific community. The External Scientific Advisory Panel recommendations will be addressed by the MLSCN Steering Group.

The PI of each center (or designee) will have one vote on the MLSCN. The NIH Science Officers may vote, and their total votes will count 1/2 as much as the total votes of the center PIs. Center membership on the Steering Group becomes effective upon issuance of the Notice of Grant Award. The Steering Group may establish additional by-laws, subcommittees, or workgroups for specific tasks. The NIH Science Officers may not chair any committee or subcommittee.

The MLSCN Steering Group meetings will be convened at least twice yearly; one of these meetings will be in conjunction with the annual meeting of the External Scientific Panel to allow the MLSCN center Directors to meet directly with the External Scientific Panel. The purpose of these meetings is to assess scientific progress, identify new research opportunities, establish priorities, consider policy recommendations, and discuss strategy. MLSCN Steering Group decisions will be made by a majority vote of a quorum, with an attempt for consensus when possible. A quorum is the presence of a majority of the center Directors and at least one Science Officer. The MLSCN Steering Group can convene through telephone conference or in person. Outside consultants/experts may be asked to participate in these discussions as nonvoting advisors. The MLSCN Steering Group may also be used to endorse HTS methods, standard operating procedures for quality control, assay validation, data analysis, and data deposition formats that will be used across multiple centers.

The MLSCN Steering Group will:

o Recommend the assignment and scheduling of assays and tasks in conjunction with the NIH Project Team.
o Develop guidelines to standardize the validation of screening data in different types of assays across centers.
o Develop uniform procedures and policies for assay validation, data quality measures, assessment procedures, and annotation conventions for data depositions in conjunction with the NIH Project Team and NCBI PubChem designee.
o Serve as a venue for coordination on improving the state-of-the-art HTS in the academic sector by reporting progress, disseminating best practices, and collectively evaluating new procedures, resources, and technologies.
o Monitor, develop, and implement quality control procedures that assure consistency across centers.
o Facilitate the timely release of data in the format and on the schedule recommended by the MLSCN Steering Group and implemented by the NIH Project Team.
o Develop and recommend progress report formats for both individual centers and for the MLSCN Program as a whole to the NIH Project Team.

Any center Director who considers a MLSCN Steering Group decision unacceptable may appeal by following the arbitration procedure described below.

7. External Scientific Panel

The External Scientific Advisory Panel will be responsible for reviewing and evaluating the progress of the MLSCN centers in meeting their individual and collective milestones and goals, and make recommendations about the progress of both the overall MLSCN Network and the

individual centers to the NIH Project Team and the MLIIG. The External Scientific Panel will provide recommendations to the NIH Project Team and the MLIIG in relation to the evolving goals of the trans-NIH Molecular Libraries and Imaging Initiative, and the accomplishments and progress of the MLSCN Network.

The External Scientific Panel will be composed of 6-8 senior non-federal advisors who are not directly involved in the activities of the MLSCN and who will be appointed by the NIH Project Team with concurrence from the MLIIG. The NIH Project Team will select one member to be the committee chair, after considering the External Scientific Panel's recommendations for chair. The chair will schedule the first meeting, develop meeting agendas, and chair the meetings. The membership of the Panel may be enlarged permanently, or on an ad hoc basis by action of the original members. The Science Officer(s) will attend the External Scientific Panel meetings as non-voting participants. Other NIH staff and MLSCN members may attend the External Scientific Panel meetings when their expertise is required for specific discussions. The External Scientific Panel will meet at least once a year. During part of this meeting, there will be a joint meeting with the MLSCN Steering Group to allow the Panel members to interact directly with the MLSCN center Directors, including the PI of the NCGC, and the PIs of the Small Molecule Repository, Coordinating Center, and PubChem. Annually, the External Scientific Panel will make recommendations regarding the overall progress of the MLSCN and the progress of the individual centers, and then provide advice regarding any changes that may be needed in the direction of the MLSCN program to the NIH Project Team and the MLIIG. The External Scientific Panel will also be consulted by the NIH Science and/or Program Officer(s) in the case that changes in a center's funding level are being considered because of poor technical performance.

8. Public Domain of Data

All awards made under this RFA are subject to the Final NIH Statement on Sharing Research Data (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html) and the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources (http://ott.od.nih.gov/NewPages/RTguide_final.html).

It is expected that research resources generated through the award will be shared by awardees according to approved sharing plans that will include, among others, the screening data, assay protocols, and materials. The plans for the development of resources for use by the biomedical community will have the appropriate timelines and mileposts. NIH program staff will evaluate the compliance with the sharing plan and scientific progress in the non-competing progress report (Form 2590); such compliance will be a criterion for continued funding of the award.

9. Intellectual Property Rights

Awardees are expected to comply with the intellectual property guidelines adopted by NIH for the MLSCN RFA. In the interim, awardees will comply with their approved plan for addressing if, or how, they will exercise their intellectual property rights, should any intellectual property be generated under a center award, while making such research resources available to the broader scientific community consistent with the goals of the NIH Molecular Libraries and Imaging Initiative. The plan will include a reasonable time frame for release of materials. This plan will also include disclosure of any pre-existing agreements involving intellectual property rights, including options to for-profit research sponsors that are associated with biomaterials and data that may be generated.

The majority of transfers to not-for-profit entities should be implemented under terms no more restrictive than the Uniform Biological Materials Transfer Agreement (UBMTA). In particular, recipients are expected to use the Simple Letter Agreement provided at

http://www.nih.gov/od/ott/RTguide_final.htm, or another document with no more restrictive terms, to readily transfer unpatented tools developed with NIH funds to other recipients for use in NIH-funded projects. If the materials are patented or licensed to an exclusive provider, other arrangements may be used, but commercialization option rights, royalty reach-through, or product reach-through rights back to the provider are inappropriate. Similarly, when for-profit entities are seeking access to NIH-funded tools for internal use purposes, recipients should ensure that the tools are transferred with the fewest encumbrances possible. The Simple Letter Agreement may be expanded for use in transferring tools to for-profit entities, or simple internal use license agreements with execution or annual use fees may be appropriate.

NIH program staff will evaluate the compliance with the sharing plan and scientific progress in the non-competing progress report (Form 2590); such compliance will be a criterion for continued funding of the award.

10. Progress Reviews/Milestones and Evaluations

The progress of the MLSCN centers will be reviewed annually by the NIH Program Officer(s), the External Scientific Panel, and the NIH Project Team to assure that satisfactory progress is being made in achieving the project objectives. During the first year of funding, and during subsequent years if deemed necessary by the Program Officer(s) and the NIH Project Team, reviews may be more frequent. The adherence of the MLSCN centers to the approved data sharing plan and intellectual property plans, which will be part of the Terms and Consitions of award, will also be reviewed annually. Should problems arise in the conduct of the study, the NIH Program Officer(s) may require that the center awardee submit quarterly reports on progress and fiscal matters.

The progress report will have two components. The first will be the standard NIH progress report (Form 2590). The second will be a more specialized report that will be developed by the MLSCN Steering Group in collaboration with the NIH Project Team. This specialized report should be included as an attachment to the standard progress report and will go to the NIH Program Officer(s) and the NIH Project Team. The contents or the report may be changed according to programmatic needs, based on discussion between NIH Program Officers, the center PI, and the MLSCN Steering Group.

The center awardees' yearly milestones will be provided to the Science Officers(s), the NIH Project Team, the MLSCN Steering Group, the MLIIG, and the External Scientific Panel. It is expected that the milestones will be adjusted annually at the award anniversary dates, both to incorporate the group's scientific accomplishments and progress, as well as to reflect any recommendations of the NIH Project Team and the External Scientific Panel. Following the review of milestones, the NIH Project Team may recommend reducing or withholding funds for any center/center project that substantially fails to meet its milestones or, if the situation warrants, augmenting any center/center project. However, simply meeting milestones may not be considered sufficient accomplishment for maintaining funding at the initially committed level. Failure to remain at state-of-the-art will also be considered grounds for reduction in funding levels.

11. Arbitration Process

Any disagreements that may arise in scientific or programmatic matters within the scope of the award between recipients and the NIH may be brought to arbitration. This special arbitration procedure in no way affects the center awardee's right to appeal an adverse action in accordance with PHS regulations 42 CFR Part 50, Subpart D and HHS regulation at 45 CFR Part 16. An Arbitration Panel will help resolve both scientific and programmatic issues that develop during the course of work that restrict progress. The Arbitration Panel will be composed of three members: a designee of the MLSCN chosen without the NIH staff voting, one designee of the NIH Project Team, and a third designee with expertise in the relevant area who is

chosen by the other two (in the case of an individual disagreement, the first member will be chosen by the individual awardee rather than by MLSCN).

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Linda Brady, Ph.D.
Project Team Leader, MLSCN
Division of Neuroscience and Basic Behavioral Science
National Institute of Mental Health
6001 Executive Boulevard, Room 7185, MSC 9641
Bethesda, MD 20892-9641
Rockville, MD 20852-9641 (for express/courier service)
Telephone: (301) 443-5288
FAX: (301) 402-4740
Email: lbrady@mail.nih.gov

o Direct your questions about peer review issues to:

Michael Kozak, Ph.D.
Division of Extramural Activities
National Institute of Mental Health
6001 Executive Boulevard, Room 6138, MSC 9608
Bethesda, MD 20892-9608
Rockville, MD 20852-9608 (for express/courier service)
Telephone: (301) 443-1340
FAX: (301) 443-4720
Email: kozakm@mail.nih.gov

Rudy Pozzatti, Ph.D.
Office of Scientific Review
National Human Genome Research Institute
Building 31, Room B2B37, MSC 2032
Bethesda, MD 20982-2032
Telephone: (301) 402-0838
FAX: (301) 435-1580
Email: Rudy_Pozzatti@nih.gov

o Direct your questions about financial or grants management matters to:

Rebecca Claycamp
Division of Extramural Activities
National Institute of Mental Health
6001 Executive Boulevard, Room 6122, MSC 9605
Bethesda, MD 20892-9604
Telephone: (301) 443-3858
FAX: (301) 443-6885
Email: rclaycam@mail.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of the proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Linda Brady, Ph.D.
Project Team Leader, MLSCN
Division of Neuroscience and Basic Behavioral Science
National Institute of Mental Health
6001 Executive Boulevard, Room 7185, MSC 9641
Bethesda, MD 20892-9641
Rockville, MD 20852-9641 (for express/courier service)
Phone: (301) 443-5288
FAX: (301) 402-4740
Email: lbrady@mail.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

Applicants are strongly encouraged to call the NIH Roadmap Project Team Leader listed under INQUIRIES with any questions regarding the responsiveness of their proposed project to the goals of this RFA. Applications for the U54 cooperative agreement are to be prepared in a manner consistent with the information presented in this RFA.

SPECIFIC INSTRUCTIONS FOR PREPARING AN APPLICATION

Applications are to be submitted on Form PHS 398 (http://grants.nih.gov/grants/funding/phs398/phs398.html). All instructions and guidelines accompanying the PHS 398 are to be followed, with the exception of the sections modified by the specific instructions described below.

It is recognized that the applications in response to this RFA will be longer and more complex than many other NIH applications. In order to ensure effective review, the application should be well organized. In particular, the five functions identified earlier in the RFA (Assay Optimization,

HTS Implementation, Synthetic Chemistry and Probe Development, Informatics, and Administration and Management) must be clearly addressed. For example, if the applicant has chosen to organize the proposed center into Cores corresponding to these functions, the Research Plan section may be divided into five corresponding sections. An applicant who has decided to organize the proposed center differently should, nevertheless, organize the application so that these functions are clearly identified.

Form Page 3: In lieu of the preprinted Table of Contents outline on Form Page 3 of PHS 398, a Table of Contents should be prepared listing the information described below.

ORGANIZATION OF THE APPLICATION:

The application should be organized as follows:

Face Page; Description, Performance Sites, and Personnel; Detailed Budget for Entire Proposed Period of Support; Introductory Overview; First Functional Unit – Detailed Budget for Initial Budget Period, Budget Justification, Biographical Sketch – Principal Investigators/Program Director, Other Biographical Sketches, Resources, Research Plan, and Appendix; Additional Functional Units (e.g., Cores 2, 3, 4, and 5) - information should be organized sequentially for each Core as indicated for the First Functional Unit.

Form Pages 4-5: The budget should be completed as described in the instruction sheet for Application for a Public Health Service Grant (Form PHS 398). Form page 4 (the detailed budget page) should be provided for each of the five functional units, and for any subcontractual or consortium agreements. A separate overall budget for the three-year project period should also be prepared using form page 4.

The budget justification beginning on PHS Form Page 5 should include a detailed justification for key personnel. As part of the justification, the percent effort that all staff are spending on each functional unit should be specified. A detailed budget justification should also be provided for any subcontractual or consortium agreements.

A detailed justification should also be supplied for equipment over $25,000 requested for the center. Equipment costs are allowable up to $500,000 in year one. Existing equipment should also be described. No limit is placed on the allowable costs for equipment in the second and third years, but equipment costs should be well justified.

INTRODUCTORY OVERVIEW (5 pages):

Provide an overview of the proposed center describing the central theme or concept and goals. Describe how the overall center can contribute to the MLSCN Research Network to achieve the overall goals of the Molecular Libraries and Imaging Initiative. Explain the proposed contribution of each of the functional units in achieving the objectives of the center.

NOTE:

Applicants to this RFA will not be expected to already have all of the necessary capabilities in place. The purpose of this RFA is to provide support for their development, so that by the end of the three-year pilot phase, centers will be fully operational and capable of providing HTS capacity to the academic scientific community.

FUNCTIONAL UNITS:

Identify each proposed functional unit by title and present the information as follows: Detailed Budget for Initial Budget Period; Budget Justification; Biographical Sketch – Principal

Investigators/Program Director; Other Biographical Sketches; Resources; Research Plan; and Appendix.

RESEARCH PLAN (50 pages overall, excluding the Introduction):

Introduction:

Provide a brief overview of the functional unit, its activities, and how the key personnel will interact and coordinate with the other functional units.

The 50-page limit for this section of the application is the total of sections A through D (specific aims, background and significance, preliminary/feasibility studies, and experimental design and methods) for all of the functional units together.

In the Research Plan section of the application, the applicant should clearly describe existing capabilities, plans for acquiring additional needed capabilities, and a clear plan for scaling up those capabilities so that by the end of the three-year pilot phase, the center will have the capacity to screen, at minimum, 100,000 compounds in 20 assays, optimized by the center for HTS, per year.

Form Page 8, Resources: Complete the resources section for each of the functional units. Describe the features of the institutional environment that are or would be relevant to the effective implementation of the proposed MLSCN program. As appropriate, describe available resources, such as equipment, cell culture facilities, laboratory facilities, participating and affiliated units, geographical distribution of space and personnel, and consultative resources. Include a letter documenting institutional commitment to the MLSCN program, including provision of funding, space, faculty positions, and/or commitments for construction or renovation. Use continuation pages as needed.

Appendix: Appendix materials are limited to a total of 10 publications directly relevant to the MLSCN program and original glossy photographs or color images provided that a photocopy is included in the Research Plan.

Supplemental Materials: Supplemental materials submitted between the application due date and the time of review are limited to a total of 2 pages per application.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at:
http://grants.nih.gov/grants/funding/phs398/labels.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, 2 additional copies of the application, including all appendix material, must be sent to:

Jean G. Noronha, Ph.D.
Molecular Libraries and Imaging Roadmap
Division of Extramural Activities
National Institute of Mental Health
6001 Executive Boulevard, Room 6154, MSC 9609
Bethesda, MD 20892-9609
Rockville, MD 20852 (for courier/express service)
Telephone: (301) 443-3367
FAX: (301) 443-4720
Email: jnoronha@mail.nih.gov

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIH Project Team. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened jointly by the Center for Scientific Review, the National Institute of Mental Health, and the National Human Genome Research Institute in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
o Receive a written critique
o Receive a second level review by the National Mental Health Advisory Council.

In addition, because of the trans-NIH nature of the Roadmap Program, all applications submitted in response to Roadmap Initiatives will be provided for informational purposes to the National Advisory Councils of all NIH Institutes and Centers.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address

and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

- Significance
- Approach
- Innovation
- Investigator
- Environment

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

A. Center as a Whole

1) The potential for impact

2) Degree of synergy, i.e., does the center as a whole serve a purpose greater than the sum of the individual components?

3) Effectiveness of the proposed center in meeting the goals of the Molecular Libraries and Imaging Initiative

B. Individual Functional Units

1) How effective is the overall organization of the proposed functional units in relation to the center's goals?

2) Will each functional unit enhance collaborative and/or interdisciplinary research within the center and the wider research community?

3) Would any proposed optional functional units duplicate existing resources or services? If so, are the requested new resources justified?

4) The quality of the facilities or services provided by this functional unit (including procedures, techniques, and quality control).

5) The qualifications, experience, and commitment of the personnel involved in the functional unit.

C. Data Management

1) Are data management and support procedures developed sufficiently to allow tracking of compounds, assays, and screening data? Are procedures in place for quality control and quality assessment for assay and screening procedures?

D. Program Administration and Management

1) Does the PI have the scientific and organizational vision and experience to serve effectively as the center Director?

2) Is there evidence of sufficient management capabilities for the center that include fiscal administration, procurement, property and personnel management, planning, and budgeting?

E. Facilities

1) Are facilities adequate for the overall functions of the center and to implement the goals of the Molecular Libraries Screening Centers Program?

G. Institutional Commitment

1) Is there evidence for institutional commitment to the program, including provision of funding, space, faculty positions, and/or commitments for construction or renovation?

2) Are the research environment and resources, including equipment and facilities, adequate? Is there potential for interaction with scientists from other departments and components?

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL REVIEW CONSIDERATIONS

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: July 26, 2004
Application Receipt Date: August 24, 2004
Peer Review Date: November/December 2004
Council Review: January/February 2005
Earliest Anticipated Start Date: March 1, 2005

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit (as determined by peer review)
o Availability of funds
o Programmatic priorities
o Programmatic balance: The purpose of the MLSCN program is to develop a network of pilot centers with complementary capabilities that will allow the network to address a wide range of biological opportunities. Therefore, decisions about awards will consider the mix of capabilities offered by the proposed centers.
o Adequacy of proposed plans for sharing data, research resources, and for exercising intellectual property rights: The goals of the MLSCN program are to make screening data publically available through PubChem and to identify/generate a diverse set of research tools (probes, assays) to explore biology and disease mechanisms. Therefore, decisions about awards will consider the responsiveness of the above-mentioned plans to the spirit of the Roadmap Initiative.

REQUIRED FEDERAL CITATIONS

ANIMAL WELFARE PROTECTION: Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf), as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm), as applicable.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include

information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and applications for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.healthypeople.gov/.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index

Return to NIH Guide Main Index

Department of Health and Human Services

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892